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Long-Term Neurologic Outcome in Children With Opsoclonus-Myoclonus Associated with Neuroblastoma: A Report From the Pediatric Oncology Group

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A retrospective data collection was performed on 29 children diagnosed with neuroblastoma and opsoclonus-myoclonus between 1983–1993 from Pediatric Oncology Group institutions. The aim was to describe neurologic outcome in children with neuroblastoma and opsoclonus-myoclonus.

Age at diagnosis ranged from one month to 4 years (median age, 18 months). The duration of opsoclonus-myoclonus symptoms prior to the diagnosis of neuroblastoma ranged from 6 days to 17 months (median duration, 6 weeks). There was a prevalence of low stage disease according to the POG staging system; stage A (n = 18), stage B (n = 3), stage C (n = 7), stage D (n = 1). There was a predominance of paraspinal primary tumors. There was no case of N-myc amplification (0/17), and 2/8 cases were diploid.

Treatment for neuroblastoma consisted of surgery alone in 19/29 (18 stage A, 1 stage C in thorax), and surgery plus chemotherapy in 10/29. No patient received radiotherapy.

Treatment for opsoclonus-myoclonus ranged varied. Six children received no treatment for opsoclonus-myoclonus. The following agents were used ACTH (n = 14), prednisone (n = 12), IV IgG (n = 6), immuran (n = 2), depakote (n = 1), and inderal (n = 1). Eighteen of 29 children (62%) had resolution of opsoclonus-myoclonus symptoms. The range of time for recovery was a few days to 3 years. However the majority recovered over several months.

Twenty of 29 children (69%) had persistent neurologic deficits including speech delay, cognitive deficits, motor delay, and behavioral problems. Of the 9 children who had complete recovery of opsoclonus-myoclonus without neurologic sequelae, age at diagnosis and duration of symptoms were not different from the entire group. Interestingly, 6/9 children with complete recovery received chemotherapy as part of their treatment. In conclusion, persistent neurologic deficits are characteristic for children with neuroblastoma and opsoclonus-myoclonus. Treatment with chemotherapy may improve the neurologic outcome. **Med. Pediatr. Oncol. 28:284–288.**

Key words: opsoclonus-myoclonus; neuroblastoma; chemotherapy

INTRODUCTION

Opsoclonus-myoclonus (OM) is a rare paraneoplastic syndrome characterized by multidirectional, chaotic eye movements, myoclonus, and ataxia. The characteristic findings of this syndrome warrant the label ''dancing eyes, dancing feet''. The OM syndrome has been associated with a variety of neoplasms including breast and ovarian carcinoma [1,2]. In children, the most common associated neoplasm is neuroblastoma. Neuroblastoma, the most common extracranial solid tumor in childhood, generally occurs in children younger than 5 years of age, with a median age at diagnosis of 2 years. It is a tumor of the sympathetic nervous system commonly occurring in the adrenal gland. Thus, the most common presentation in children is the discovery of an abdominal mass. Unfortunately, the majority of children with neuroblastoma have metastatic disease at diagnosis, and consequently experience unfavorable outcomes. The overall incidence of OM in children with neuroblastoma is approximately 3%. There is evidence that children with neuroblastoma and opsoclonus-myoclonus have a good prognosis for survival [1]. However the prognosis for full neurologic recovery has not been well studied.

We report the results of a retrospective survey of children with OM and neuroblastoma from Pediatric Oncology Group institutions. The aim was to identify both neurologic outcome in these children, and the outcome in regard to the OM.

METHODS

An initial survey of POG institutions was obtained to assess the overall incidence of OM with neuroblastoma

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TABLE I. The POG Staging System for Neuroblastoma

Stage A	Complete gross excision of primary tumor, margins histologically negative or positive. Intracavitary lymph nodes not intimately adhered to tumor are removed and are histologically free of tumor. Liver histologically free of tumor.
Stage B	Incomplete gross resection of primary tumor. Lymph nodes and liver as in Stage A.
Stage C	Complete or incomplete resection of primary tumor. Intracavitary lymph nodes histologically positive for tumor. No metastatic disease.
Stage D	Metastatic disease.

and the potential interest in a therapeutic study. Institutions were asked to identify the number of children diagnosed with OM and neuroblastoma in a ten-year period 1983–1993. Follow-up data sheets were sent to the institutions which identified patients with OM and neuroblastoma. The data obtained included date of birth, gender, age at diagnosis, year diagnosed, duration of symptoms prior to diagnosis, biologic markers, histology, stage, location of primary, and metastatic sites, treatment for neuroblastoma, treatment for opsoclonus-myoclonus, duration of OM symptoms post diagnosis, and current neurologic state of the child, specifically in regard to speech delay, motor delay, seizures, behavioral problems, cognitive deficits, or other neurologic deficits. DNA ploidy and N-myc amplification analysis were performed on a subset of children in POG reference laboratories as previously described [3]. Ten children in this study have been previously reported [4].

RESULTS

Fifty of the 95 POG institutions responded to the initial survey. Of these 50 institutions, 27 reported that they had not seen a case of OM in the past 10 years. Fourteen of the remaining 23 institutions completed data sheets on their patients with neuroblastoma and OM. Overall, data was collected for 29 children with neuroblastoma and OM from 14 different institutions, and comprise the study group for this report.

There were 15 males and 14 females. The age at diagnosis ranged from 1 month to 4 years with a median age of 18.0 months. The duration of symptoms of OM prior to diagnosis ranged from 6 days to 17 months with a median duration of 6 weeks. Eight children had symptoms for less than two weeks, and 5 children had symptoms for more than three months. Median time of follow-up was 3 years, with a range of 6 months to 13 years.

Children were staged according to the POG staging system (table I). Eighteen children were stage A, 3 children were stage B, 7 children were stage C, and one child had stage D disease. The primary tumor site was the mediastinum in 9 children, the adrenal gland in 7 children, and the lumbosacral paraspinal region in 12 children. One child had primary tumor site in the neck.

TABLE II. Treatment for Neuroblastoma

Treatment modality	Number of patients (n = 29)
Surgery only	19
Surgery plus chemotherapy[a]	10
Radiation therapy	0

[a]7 with oral cyclophosphamide and doxorubicin, 1 with MADDOC (nitrogen mustard, doxorubicin, DTIC, cisplatin, vincristine, cyclophosphamide, 2 with CECA (cisplatin, etoposide, cyclophosphamide, doxorubicin)

Sixteen children were registered on POG biologic and therapeutic protocols. Biologic markers (N-myc copy number, DNA index, ferritin) were obtained in the majority of children. Of the seventeen children with data on N-myc copy number, all showed a single copy N-myc. DNA index was performed in 10 children and 8 were hyperdiploid, 2 were diploid. Serum ferritin at diagnosis was performed in 10 children, and was elevated only in 2 children. The 2 children with elevated ferritin (greater than 142 ng/mL) did not have N-myc copy number or DNA index performed. Histologic diagnosis showed neuroblastoma in 18 children, and ganglioneuroblastoma in 9 children, and was unknown in 2. Regional lymph node examination was positive for tumor in 4 children, negative in 5 children, and unknown in 10 children.

Treatment for neuroblastoma was determined by stage, and is described for all patients in table II. Children received chemotherapy based on the stage of their disease. No child received radiation therapy.

Treatment for the OM syndrome varied dramatically and is described in table III. Overall, 15 children received only one mode of treatment for OM, 4 children received 2 different therapies, 2 children received 3 therapies, and 2 children received 4 different therapies.

Overall, at the time of the study 11 of 29 children had persistent symptoms of OM. Neurologic outcome was abnormal in 20 of 29 children (table IV). A two-sided Fisher's Exact Test was done with 10 children who received chemotherapy and 19 children who did not received chemotherapy testing for 1) resolution of OM symptoms and 2) complete neurologic recovery. The analysis for resolution of OM symptoms produced a p value of 0.004. The analysis for complete neurologic recovery produced a p value of 0.03.

The neurologic problems that developed in these children were significant and multiple. Motor delay was the most prevalent problem, but many children experienced more global neurologic problems with cognitive deficit, speech delay and behavioral problems. For example, patient #22 was diagnosed at 17 months of age with stage A neuroblastoma. At 4 years from diagnosis this child was severely ataxic, requiring ambulatory assistance, had minimal speech and was in special education. Behavioral

TABLE III. Treatment for Opsoclonus-Myoclonus for all Patients and Treatment for the 9 Patients With Complete Neurologic Recovery and Resolution of Opsoclonus-Myoclonus Symptoms

Treatment of OM	Number of patients (n = 29)	Number of patients with complete neurologic recovery and resolution of OM (n = 9)	
		Received chemotherapy	Did not receive chemotherapy
None	6	2	0
ACTH	14	0	2
Oral prednisone	12	2	1
IV IgG	6	2	0
Immuran	2	0	0
Depakote	1	0	0
Inderal	1	0	0

problems were severe enough in some children to require trials of anti-psychotic medications.

DISCUSSION

This report describes the clinical characteristics and outcome in 29 children with neuroblastoma and the syndrome of OM. The typical characteristics of neuroblastoma differ in children who showed presence of the unusual syndrome of OM. The median age of diagnosis in our group of 29 children was 18 months, slightly younger than the average for neuroblastoma which is 2 years of age [5]. The primary tumor site was not the adrenal gland, but rather there was a predominance of tumors that occurred in the mediastinum and lumbosacral paraspinal region. The majority of children (62%) had POG stage A tumors, compared with 10% among children with neuroblastoma in general [5]. These characteristics of localized, low stage disease, have been noted in children with neuroblastoma and OM [6].

The incidence of OM with neuroblastoma is reported to be 2–3% of all children with neuroblastoma [6]. It is difficult to estimate an incidence rate from our study, since not all institutions responded to our initial survey. However, the information from our study which is interesting is the fact that more cases were diagnosed in the 1990s than in the 1980s. This finding may be indicative of better diagnostic procedures, since many of the tumors are small, localized lesions near the spine. With functional imaging (metaiodobenzylguanidine scintigraphy) and magnetic resonance imaging, some tumors may have been diagnosed, which previously would have been missed.

Although biologic studies were not obtained in all cases, there is some information on 18 of the 29 children. The results were consistent with favorable disease, with no cases of N-myc amplification, only 2 diploid cases, and 2 cases of elevated serum ferritin. There were 9 cases of ganglioneuroblastoma, again a biologically favorable prognostic marker. Cohn et. al. examined 4 cases of neuroblastoma tissue in children with OM and each case showed single copy of N-myc, again consistent with biologically favorable disease [7].

The outcome with regard to survival for children with neuroblastoma and OM is favorable. This fact was also true in our series. There was only one death in our series. A 29-month-old who had stage D neuroblastoma with bone marrow involvement, died of fungal sepsis. What has been less clear in large series is the neurologic outcome for these children.

There are 3 published series of children with the OM syndrome and neuroblastoma. A study of 10 children from a single institution over a 17-year time span demonstrated the morbidity for children with neuroblastoma and OM [8]. Although the survival rate was 100%, nine of 10 children had neurologic sequelae including cognitive deficits, speech delay, behavioral problems, seizures, and problems with coordination. None of the children in this study received chemotherapy. As in our study, these investigators could find no correlation between duration of symptoms of OM prior to the diagnosis and neurologic outcome.

A second series described the case reviews of 5 children with neuroblastoma and OM presenting to a single institution over a 6-year span [9]. Survival and tumor-free survival for these children was excellent. Four of the 5 children had localized disease and received surgery only. Each child had neurologic sequelae. The children had global developmental delay, speech delay, and motor delay. One child received 2 years of chemotherapy because of lymph node involvement. This child had complete neurologic recovery.

A third series reported the long term outcome in 10 children [4]. Only 1 child had neurologic recovery, although all children were tumor-free. The neurologic outcomes were significant and similar to those noted in our group of patients. Development delay and behavioral problems were noted in 9 of the 10 children, and in addition, motor delay and ataxia was noted in 6 of the 10 children. Only two of these children received adjuvant therapy, one received 2000 cGy of local radiation therapy and one child received a single 3-day course of cyclophosphamide and doxorubicin.

In our series of 29 children with median follow-up of 3 years, 11 children had persistence of OM symptoms. Twenty of the 29 children had neurologic sequelae. The sequelae are significant, and clearly affect quality of life. Many children have speech and motor delay. Additionally, these children experienced behavioral problems, cognitive deficits, and global developmental delay. It is difficult to say if the behavioral problems experienced by these children are a result of OM directly, or a consequence of coping with devastating effects of OM. Neither

TABLE IV. Neurologic Outcome

Patient #	Age (months)	Stage	Persistent of OM	Neurologic outcome	Chemotherapy
1	18	A	yes	Motor delay Speech delay	None
2	10	C	no	Normal	MADDOC
3	12	A	yes	Speech delay Cognitive delay	None
4	12	A	yes	Motor delay	None
5	27	A	no	Speech delay	None
6	8	C	no	Motor delay Cognitive delay	None
7	30	A	yes	Speech delay Cognitive delay Motor delay	None
8	17	A	yes	Development delay	None
9	12	A	no	Normal	None
10	9	A	no	Speech delay Motor delay	None
11	18	A	no	Speech delay	None
12	48	B	no	Cognitive delay	C/A
13	29	D	no	Speech delay Motor delay	CECA
14	24	A	yes	Speech delay Behavioral problems Motor delay	None
15	12	C	no	Normal	C/A
16	15	A	yes	Speech delay Cognitive delay Motor delay	None
17	23	C	no	Normal	C/A
18	23	C	no	Normal	C/A
19	17	A	no	Normal	None
20	1	C	no	Motor delay	C/A
21	18	B	no	Motor delay	C/A
22	17	A	yes	Speech delay Cognitive delay Motor delay Behavioral problems	None
23	31	A	yes	Speech delay Cognitive delay Motor delay Behavioral problems	None
24	20	A	no	Normal	None
25	21	A	no	Speech delay Cognitive delay Motor delay	None
26	36	A	yes	Motor delay Behavioral problems	None
27	19	A	yes	Cognitive delay Motor delay Behavioral problems	None
28	17	B	no	Normal	C/A
29	21	C	no	Normal	CECA

age at diagnosis, duration of symptoms of OM prior to diagnosis, histology nor treatment of the OM symptoms (i.e. ACTH, oral steroids) were prognostic factors in regard to neurologic outcome or persistence of OM symptoms (data not shown).

The prognostic factor for neurologic outcome was treatment of the tumor. In particular, treatment with chemotherapy seem to benefit children in regard to neurologic outcome. Ten children in this study were treated with chemotherapy, all of whom had resolution of the OM symptoms, and 6/10 had no neurologic sequelae. In contrast, of the 19 children who did not receive chemotherapy because they had stage A disease, only eight had resolution of OM symptoms ($p = 0.004$), and only three

had no neurologic sequelae ($p = 0.03$). All the chemotherapy regimens were relatively immunosuppressive. Seven children received cyclophosphamide and doxorubicin. The other regimens (2-cyclophosphamide, doxirubicin, cisplatin, etoposide, and 1-nitrogen mustard, doxorubicin, DTIC, cisplatin, vincristine, cyclophosphamide) contain cyclophosphamide and are intensive immunosuppressive and myelosuppressive combinations.

It is intriguing that chemotherapy may improve the neurologic outcome for children with neuroblastoma and OM. The mechanism may be related to the immunosuppression from chemotherapy [10]. The etiology of the OM syndrome is thought to have an immune basis. A study of 10 women with paraneoplastic cerebellar degeneration secondary to gynecological carcinomas demonstrated production of an anti-tumor antibody production [11]. The investigators showed the presence of an anti-Purkinje-cell antibody, anti-Yo, in the tumors from these women. By Western blot assay and immunohistochemistry, Yo antigen was expressed in tumor tissue from women with the neurologic syndrome, while tumor tissue from women without the neurologic syndrome showed no expression of the Yo antigen. The implication is that the tumor cells produced an anti-onconeural response. If so, the immunosuppression from chemotherapy may diminish the production of this antibody and thus improve the neurologic outcome.

There is other evidence that the pathophysiology of OM is immune-mediated. As with other autoimmune diseases, investigators have explored the use of intravenous gamma globulin (IV IgG) in children with OM [12,13]. Two reports suggest that high doses of IV IgG can improve symptoms presumably by inhibiting antibody activity. Six patients in our series treated with IV IgG received various doses and schedules. Only two children had complete recovery, but these was also two children who received chemotherapy.

In conclusion, children with neuroblastoma and OM have excellent long-term survival and the majority do have resolution of OM symptoms. However, 69% of the group have significant, long-term neurologic deficits. The children who received chemotherapy seem to have a better neurologic outcome, and the explanation may involve the immunosuppression from chemotherapy.

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